Synthesis of Proposed Chain-Elongation Intermediates of the Monensin Biosynthetic Pathway

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Three proposed intermediates of the monensin biosynthetic pathway have been synthesized in ^{13}C-labeled form. Treatment of [2-^{13}C]propionyl *N*-acetylcysteamine (NAC) thioester **10** with 2 equiv of LDA followed by acylation with [1-^{13}C]acetyl chloride gave racemic [2,3-$^{13}C_2$]-2-methyl-3-ketobutyryl NAC thioester (**9**). Ireland enolate Claisen rearrangement of the [1,2-$^{13}C_2$]-labeled acetate ester **12** gave the allylsilane **13**. Metalation-alkylation of the derived 4(*S*)-(−)-benzyloxazolidinone imide **14** followed by removal of the chiral auxilliary gave the enantiomerically pure acid **16**, which underwent intramolecular protodesilylation to give the olefinic acid (+)-**17** consisting of 90% of the desired 2*S*,4*R* diastereomer. Treatment of **17** with mercuric acetate followed by lithium tetrachloropalladate gave the enol lactone **19**, which was readily converted to (2*S*,4*R*)-[1,2-$^{13}C_2$]-2,4-dimethyl-5-oxohexanoyl NAC thioester (**20**) by exposure to *N*-acetylcysteamine in the presence of base. The synthesis of (2*E*)-(4*S*,6*R*)-[1,2-$^{13}C_2$]-4,6-dimethyl-7-oxo-2-octenoyl NAC thioester **27** was achieved by two step reduction of unlabeled (+)-**17** to the aldehyde **22**, followed by Wittig olefination with [1,2-$^{13}C_2$]carbomethoxymethylenetriphenylphosphorane, hydrolysis, and thioesterification.

Monensin A (**1**) is the most widely used and probably the best studied representative of the anticoccidial polyether metabolites.[1] While it has been proven that the carbon skeleton of **1** is derived from units of acetate, propionate, and butyrate, and the origins of each of the oxygen atoms of monensin have been established,[2,3] very little is known about the method of skeletal construction for this or any other polyether, nor have any of the relevant biosynthetic enzymes been isolated. In 1983, we proposed a unified mechanism for the biosynthesis of polyether antibiotics, based on the cascade cyclization of a postulated polyepoxide intermediate.[4] If the formation of the polyketide chain of monensin were to be analogous to fatty acid biosynthesis, then the necessary units of acetate, propionate, and butyrate should be condensed sequentially, with concurrent adjustment of oxidation and unsaturation, as illustrated in Scheme I. Thus **2**–**4** represent plausible five-carbon, eight-carbon, and ten-carbon polyketide chain elongation intermediates, while premonensin (**5**) corresponds to the proposed triene intermediate.[4-6]

Recently it has been found that thioester derivatives of presumed chain elongation intermediates can be incorporated by intact cells into macrolide antibiotics without prior degradation. For example, both a six-carbon propionate–propionate and nine-carbon tripropionate precursor have been incorporated as the corresponding *N*-acetylcysteamine (NAC) thioesters into tylactone by cultures of *Streptomyces fradiae*.[7] Similarly the NAC thioester of a six-carbon propionate–propionate intermediate has been incorporated into erythromycin by *Saccharopolyspora erythraea* (formerly *Streptomyces erythreus*).[8] In order to carry out analogous studies of the early stages of monensin biosynthesis, we needed to develop convenient preparations of the NAC thioesters of the five-carbon acetate–propionate (AP), eight-carbon acetate–propionate–propionate (APP), and ten-carbon acetate–propionate–propionate–acetate (APPA) intermediates corresponding to **2**–**4**. Ideally, the synthetic routes chosen would allow for the preparation of each of these substrates in enantiomerically pure form and bearing multiple ^{13}C labels at appropriate positions.

Results

The racemic AP *N*-acetylcysteamine derivative **9**, with two ^{13}C labels spanning the acetate–propionate junction, was synthesized as shown in Scheme II. In our initial approach, ethyl [2,3-$^{13}C_2$]acetoacetate (**6**), synthesized from [1-^{13}C]acetyl chloride and monopotassium [2-^{13}C]ethylmalonate, was methylated in 95% yield via the thallium enolate.[9] Although the ester **7** could be readily hydrolyzed with aqueous alkali, the free acid proved to be very susceptible to decarboxylation, and all attempts to form the thioester **9** from the free acid, using standard conditions, resulted in extremely low yields. It was found, however, that the lithium salt **8** resulting from hydrolysis of **7** could be converted directly, albeit in low yield, to the thioester **9** by treatment with *N*-acetylcysteamine and diphenyl phosphorazidate.

Since the yield for the conversion of **7** to **9** was only 11%, an alternative approach was developed. The NAC [2-^{13}C]propionyl thioester **10** was readily synthesized from sodium [2-^{13}C]propionate via the acid chloride in 55% yield. Treatment of **10** with 2 equiv of LDA and quenching of the resulting dilithio derivative with [1-^{13}C]acetyl chloride led directly to the formation of the target NAC thioester **9** in 33% yield (40% yield based on recovered starting material). Some material resulting from carbon and nitrogen bisacylation was also isolated, which could be converted to the desired product by trans-thioesterification with *N*-acetylcysteamine. This very simple route allowed rapid access to useful quantities of racemic [2,3-$^{13}C_2$]-2-methyl-3-oxobutyryl NAC thioester (**9**) corresponding to the desired AP intermediate.

The synthesis of the desired APP and APPA intermediates was based on the convenient preparation of the olefinic acid (+)-**17** in both labeled and unlabeled form. Acetylation of the allylic alcohol **11** with [1,2-$^{13}C_2$]acetyl

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(2) (a) Cane, D. E.; Liang, T. C.; Hasler, H. *J. Am. Chem. Soc.* **1981**, *103*, 5962. (b) Cane, D. E.; Liang, T. C.; Hasler, H. *J. Am. Chem. Soc.* **1982**, *104*, 7274.
(3) Ajaz, A.; Robinson, J. A. *J. Chem. Soc., Chem. Commun.* **1983**, 679.
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(5) Van Middlesworth, F.; Patel, D. V.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2996.
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(8) Cane, D. E.; Yang, C.-C. *J. Am. Chem. Soc.* **1987**, *109*, 1255.
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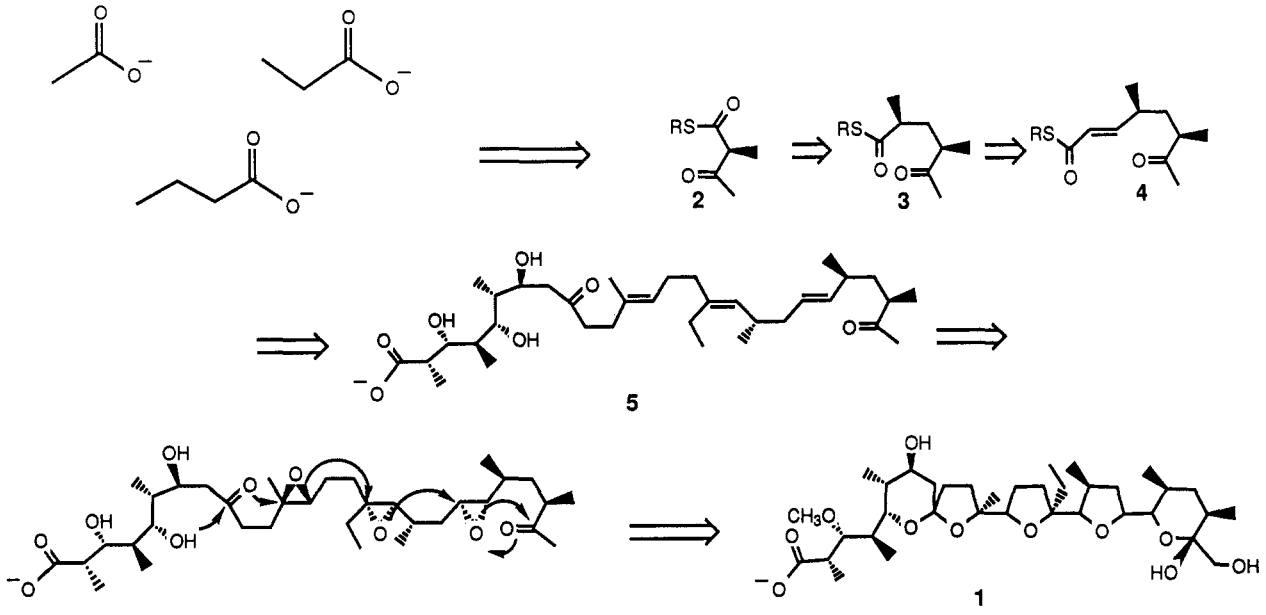
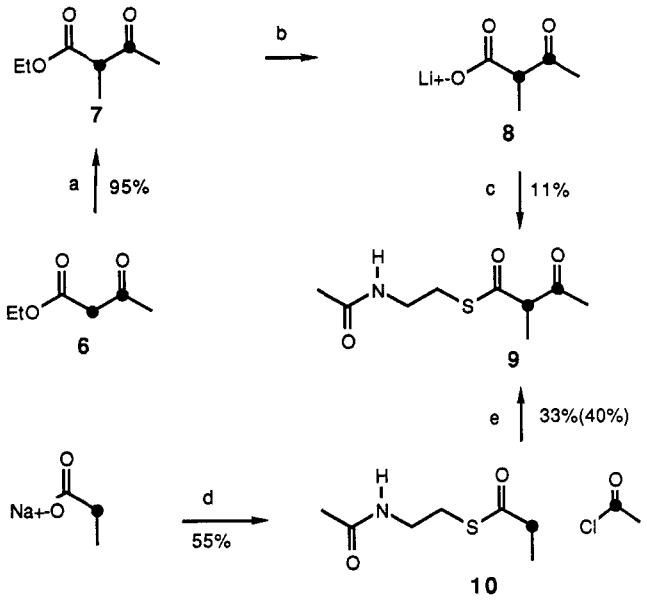
Scheme I



Scheme II[a]



[a] (a) TlOEt, MeI; (b) 1 N LiOH; (c) NAC–SH, $(PhO)_2PON_3$; (d) phthaloyl dichloride, NAC–SH; (e) LDA.

chloride gave [1′,2′-$^{13}C_2$]-**12** in quantitative yield. Ireland enolate Claisen rearrangement of **12** in the presence of HMPA produced the allylsilane **13** in yields of 50–75% (Scheme III). Conversion of **13** to the (*S*)-(−)-benzyloxazolidinone derivative **14** was effected in 72% yield through the intermediacy of the corresponding acylimidazole. Treatment of **17** with LDA followed by alkylation with methyl iodide allowed introduction of the 2-methyl substituent in 69% yield with the correct absolute configuration.[10,11] Removal of the chiral auxilliary by treatment with lithium hydroxide in hydrogen peroxide gave the enantiomerically pure acid **16** in 97% yield.[12]

Subsequent protodesilylation of **16** with boron trifluoride–acetic acid complex, as previously described by Wilson,[13] gave the desired olefinic acid (+)-**17** as an 8:1 mixture of the 2*S*,4*R* and 2*S*,4*S* diastereomers, as determined by ^{1}H NMR and ^{13}C NMR analysis.[13] The absolute configuration of (+)-**17** was confirmed by esterification with diazomethane of a sample of unlabeled (−)-**17** (derived from the corresponding (*R*)-(−)-benzyloxazolidinonimide) followed by $RuCl_3$–$NaIO_4$ oxidation to the known (2*R*,4*S*)-(−)-monomethyl 2,4-dimethylglutarate (**18**).[14]

Treatment of (+)-**17** with mercuric acetate followed by reaction with lithium tetrachloropalladate under anhydrous conditions[15,16] gave the enol lactone **19** in 30% yield. Although a variety of conditions could be used for the enol lactonization, higher yields were not obtained. Ring opening of **19** with *N*-acetylcysteamine in the presence of DBU gave a 70% yield of the desired APP intermediate, (2*S*,4*R*)-[1,2-$^{13}C_2$]-2,4-dimethyl-5-oxohexanoyl NAC thioester (**20**) as an 8:1 mixture with the minor 2*S*,4*S* diastereomer. The diastereomeric purity of **20** was determined by ^{13}C NMR analysis, which indicated that no loss of stereochemical purity had occurred during the conversion of (+)-**17** to (+)-**20**. It should be noted that variation of the thiol derivative used in the opening of the enol lactone should allow convenient access to a wide variety of thioester derivatives of the APP intermediate.

The desired 1,2-$^{13}C_2$-labeled APPA NAC thioester **27** was synthesized as an 8:1 mixture of diastereomers directly from unlabeled olefinic acid (+)-**17** (Scheme IV). Conversion of **17** to the amide **21** followed by Dibal reduction[17] and careful hydrolysis with pH 7.4 buffer gave the volatile aldehyde **22**, which was reacted immediately with the Wittig reagent **23**, conveniently prepared from commercially available [1,2-$^{13}C_2$]bromoacetic acid. The resulting α,β-unsaturated ester **24** was obtained in 45% overall yield

(10) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am.* Chem. *Soc.* **1982**, *104*, 1737.
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(13) (a) Wilson, S. R.; Price, M. F. *J. Am. Chem. Soc.* **1982**, *104*, 1124. (b) Attempts to resolve (±)-**16** or (±)-**17** as the derived α-methylbenzylamine salts were unsuccessful.
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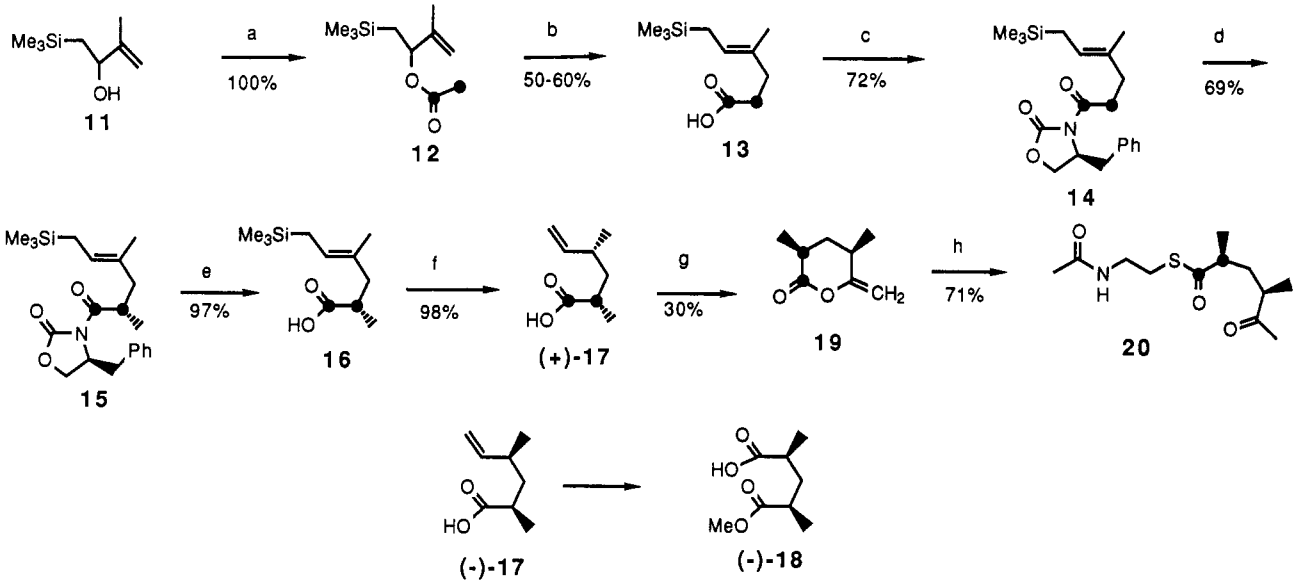
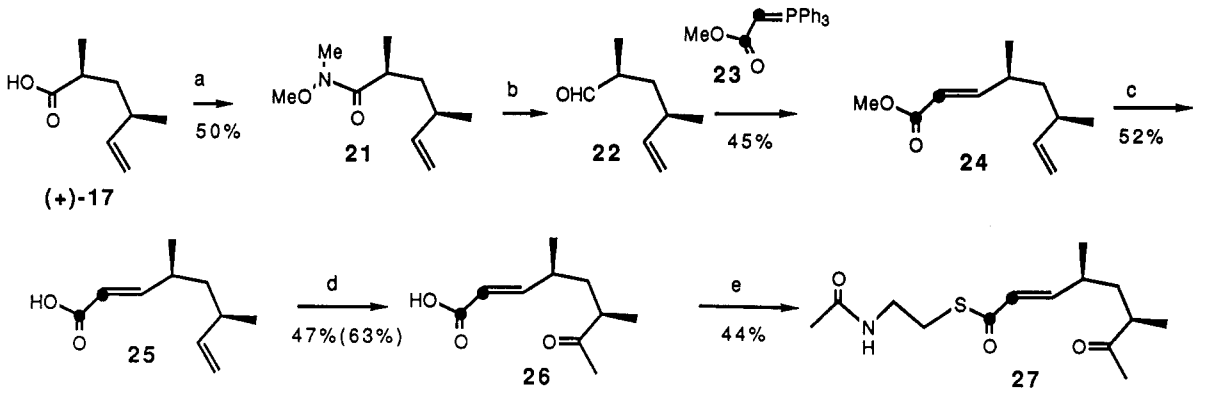
Scheme III[a]



[a] (a) CH_3COCl, pyr; (b) LDA, HMPA, TBDMSCl, HCl; (c) carbonyl diimidazole, (*s*)-(−)-benzyl oxazolidinone, LDA; (d) LDA, MeI; (e) LiOH, H_2O_2; (f) BF_3AcOH; (g) $Hg(OAc)_2$, Li_2PdCl_4; (h) NAC–SH, DBU.

Scheme IV[a]



[a] (a) Carbonyl diimidazole, (MeO)MeNH, Et_3N; (b) Dibal; (c) KOH; (d) $Hg(OAc)_2$, Li_2PdCl_4; (e) NAC–SH, $(PhO)_2PON_3$, Et_3N.

from the amide. Alkaline hydrolysis of **24** and selective reaction of the terminal alkene with mercuric acetate and lithium tetrachloropalladate gave the methyl ketone **26** in 47% yield (63% based on recovered starting material).[16] The desired (2*E*)-(4*S*,6*R*)-[1,2-$^{13}C_2$]-4,6-dimethyl-7-oxo-2-octenoyl NAC thioester (**27**) was obtained as an 8:1 mixture with the corresponding 4*S*,6*R* diastereomer by treatment of **26** with diphenyl phosphorazidate in the presence of *N*-acetylcysteamine and triethylamine. NMR analysis of each synthetic intermediate indicated that no undesired epimerization of the C-2 or C-4 methyl groups had occurred during the conversion of **17** to **27**.

Conclusion

We have developed versatile synthetic routes to the NAC thioesters of the proposed five-, eight-, and ten-carbon chain elongation intermediates of monensin biosynthesis. These substrates are also potential precursors of numerous additional APPA-type polyethers,[1] including nigericin, etheromycin, septamycin, mutalomycin, and lenoremycin.[4] The synthetic approaches described above are suitable for convenient introduction of isotopic labels at a variety of positions, while simple variation of the final steps can generate a range of thioester derivatives. The availability of NAC thioesters corresponding to **3** and **4** in high diastereomeric and enantiomeric purity will facilitate further investigation of the chain-elongation steps of polyether biosynthesis. The results of these studies, now in progress, will be reported in due course.

Experimental Section

Instrumentation. NMR spectra were obtained at 400.0 or 250.0 MHz (^1H) and 100.6 or 62.9 MHz (^{13}C), respectively. Spectroscopic and high-resolution mass spectrometric data reported are for the parent unlabeled compounds except where specifically noted. The NMR spectra of the corresponding ^{13}C-labeled isotopomers showed the expected ^1H–^{13}C couplings and ^{13}C enhancements. The purity of all title compounds submitted for high-resolution mass spectrometric analysis was determined to be ≥90–95% by ^1H NMR, ^{13}C NMR, and TLC analyses. Optical rotations were measured with a 10 cm path length cell. All ^{13}C-labeled reagents were 99 atom % enriched.

[2-^{13}C]Propionyl *N*-Acetylcysteamine Thioester (10). Sodium [2-^{13}C]propionate (0.5 g, 5.15 mmol) and phthaloyl dichloride (5 mL) were placed in a 10-mL round-bottom flask, which was connected via a right-angle glass tube to a 50-mL two-neck flask. The system was sealed with Teflon tape and placed under an atmosphere of nitrogen. The two-neck flask was cooled in a dry ice–acetone bath, and the reaction flask was heated at 170–180 °C for 1 h. At this point all the [2-^{13}C]propionyl chloride had distilled into the two-neck flask, which was disconnected and sealed with a septum.

A solution of *N*-acetylcysteamine (550 mg, 5.15 mmol) and triethylamine (1.04 g, 10.3 mmol) in diethyl ether (35 mL) was added by syringe to the [2-^{13}C]propionyl chloride, with cooling of the reaction mixture in an ice bath. The mixture was stirred at room temperature for 12 h, poured into 40 mL of aqueous NH_4Cl, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography on silica using ethyl acetate–pentane (3:1) as eluent gave [2-^{13}C]-**10** as a clear, colorless oil (464 mg, 51%): ^{1}H NMR ($CDCl_3$) δ 1.01 (3 H, dt, J_{CCH} = 4 Hz, J = 7 Hz, $CH_3{}^{13}CH_2$), 1.82 (3 H, s, CH_3CO), 2.44 (2 H, dq, J_{CH} = 85 Hz, J = 7 Hz, $^{13}CH_2$), 2.87 (2 H, t, J = 6 Hz, CH_2S), 3.25 (2 H, q, J = 6 Hz, CH_2NH), 6.7 (1 H, br s, N*H*); ^{13}C NMR ($CDCl_3$) δ 37.08 ($^{13}CH_2$); EI mass spectrum, *m/e* 176.0732 (calcd for $C_7H_{14}NO_2S$ [M + H] 176.07451).

[2,3-$^{13}C_2$]-2-Methyl-3-oxobutyryl *N*-Acetylcysteamine Thioester (9). Diisopropylamine (0.74 mL, 533 mg, 5.27 mmol) was dissolved in THF (40 mL) and cooled to 0 °C. *n*-Butyllithium (1.6 M, 3.3 mL, 5.27 mmol) was added, and the reaction mixture was stirred for 20 min and cooled to −78 °C. The [2-^{13}C]propionyl thioester **10** (464 mg, 2.63 mmol) in THF (10 mL) was added followed after 20 min by [2-^{13}C]acetyl chloride (0.187 mL, 207 mg, 2.65 mmol). The reaction mixture was warmed to room temperature, and ethyl acetate (40 mL) was added. The organic solution was washed with NH_4Cl solution (40 mL), water (2 × 40 mL), and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography on silica (30% acetone in methylene chloride) gave [2,3-^{13}C]-**9** as a clear, colorless oil (190 mg, 33%), along with starting material **10** (75 mg; yield based on recovered starting material is 40%) and bisacylated material (240 mg): ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, m, $CH_3{}^{13}CH$), 1.70 (3 H, s, CH_3CO), 2.19 (3 H, dd, J_{CCH} = 8 Hz, J_{CCCH} = 1 Hz, $CH_3{}^{13}CO$), 3.00 (2 H, m, CH_2S), 3.37 (2 H, m, CH_2NH), 3.75 (1 H, dm, ^{13}CH), 6.3 (1 H, br s, N*H*); ^{13}C NMR ($CDCl_3$) δ 61.91 (d, J = 38 Hz, ^{13}CH), 202.66 (d, J = 38 Hz, ^{13}CO); EI mass spectrum, *m/e* 218.0838 (calcd for $C_9H_{16}NO_3S$ [M + H] 218.08507).

1-(Trimethylsilyl)-2-acetoxy-3-methyl-3-butene (12). Sodium acetate (3.0 g, 36.2 mmol) and phthaloyl dichloride (5 mL) were converted to acetyl chloride (2.24 g, 78%) by the method described above for the preparation of propionyl chloride. The same procedure was used to generate [1,2-$^{13}C_2$]acetyl chloride from sodium [1,2-$^{13}C_2$]acetate (99 atom % ^{13}C).

A solution of the allylic alcohol **11** (4.42 g, 28.0 mmol) and pyridine (4.7 mL, 4.39 g, 5.56 mmol) in diethyl ether (35 mL) was added by syringe to the acetyl chloride (28.5 mmol) with cooling of the reaction mixture in an ice bath. The mixture was then stirred at room temperature for 12 h, poured into 40 mL of aqueous NH_4Cl, and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with NH_4Cl solution (2 × 20 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to give the known ester **12**[13] as a clear colorless oil (5.73 g, 100%): ^{1}H NMR ($CDCl_3$) δ 0.00 (9 H, s, $Si(CH_3)_3$), 0.99 (1 H, dd, J = 8, 15 Hz, CH_aH_bSi), 1.08 (1 H, dd, J = 8, 15 Hz, CH_aH_bSi), 1.70 (3 H, s, CH_3), 2.00 (3 H, s, CH_3CO), 4.80 (1 H, s, C*H*), 4.95 (1 H, s, C*H*), 5.35 (1 H, t, J = 9 Hz, C*H*O); ^{1}H NMR [1′,2′-$^{13}C_2$]-**12** ($CDCl_3$) δ 2.0 (3 H, dd, J_{CCH} = 8 Hz, J_{CH} = 160 Hz, $^{13}CH_3{}^{13}CO$).

(4*E*)-4-Methyl-6-(trimethylsilyl)-4-hexenoic Acid (13). A solution of diisopropylamine (4.35 mL, 3.14 g, 31.0 mmol) in THF (40 mL) was stirred and cooled at 0 °C under argon as freshly titrated *n*-butyllithium (2.15 M, 14.4 mL, 29.6 mmol) was added slowly, while the temperature was kept below 6 °C. After a further 15 min the reaction was cooled to −78 °C in a dry ice–acetone bath. HMPA (5 mL) was added, and after 10 min a solution of 5.73 g (28.2 mmol) of the ester **12** and 4.7 g (31.0 mmol) of TBDMSCl in THF (5 mL) was added slowly, keeping the temperature below −65 °C. After 15 min the reaction mixture was allowed to warm to room temperature and was stirred for a further 3 h. The reaction mixture was then poured into diethyl ether (200 mL) and washed with water (2 × 100 mL) and 100 mL of aqueous NH_4Cl. The organic layer was concentrated and taken up in THF (80 mL) and 20 mL of 1 M HCl. The mixture was stirred for 1 h and then poured into ethyl acetate (200 mL), washed with NH_4Cl solution (50 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting oil was placed under high vacuum for 12 h to remove the *tert*-butyldimethylsilyl alcohol. Chromatography on silica gel using a 10%–50% ethyl acetate–pentane gradient as eluent gave the acid **13** as a clear colorless oil (3.20 g, 56%): ^{1}H NMR ($CDCl_3$) δ −0.1 (9 H, s, $Si(CH_3)_3$), 1.37 (2 H, d, J = 13 Hz, CH_2Si), 1.55 (3 H, s, CH_3), 2.25–2.50 (4 H, m, CH_2CH_2), 5.20 (1 H, t, J = 13 Hz, C*H*); IR λ_{max} ($CHCl_3$) 3200–2800 (CO_2H), 1710 (C=O) cm^{-1}; EI mass spectrum, *m/e* 200.1239 (calcd for $C_{10}H_{20}O_2Si$ 200.12325).

4(*S*)-Benzyl-*N*-[4′-methyl-6′-(trimethylsilyl)-4′-hexenoyl]oxazolidinone (14). A solution of 3.46 g (17.0 mmol) of the acid **13** and 2.76 g (17.0 mmol) of carbonyl diimidazole in THF (25 mL) was heated at reflux under argon for 1 h. The resulting solution of acyl imidazole was cooled to −78 °C in a dry ice–acetone bath. 4(*S*)-(−)-Benzyloxazolidinone (3.02 g, 17.0 mmol) was dissolved in THF (50 mL), and the solution was cooled to −78 °C under an atmosphere of argon. *n*-Butyllithium (2.15 M, 8.05 mL, 17.3 mmol) was added, and the reaction mixture was stirred for 20 min. The cooled solution of acylimidazole was transferred as rapidly as possible to the reaction flask via a double-ended needle. The reaction mixture was then allowed to warm to room temperature and stirred for a further 1 h before being poured into ethyl acetate (150 mL), washed with NH_4Cl solution (2 × 40 mL), sodium bicarbonate solution (40 mL), and brine (40 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica gel, using 10% ethyl acetate–pentane as eluent, gave the (*S*)-(−)-benzyloxazolidinone derivative **14** as a clear colorless oil (4.436 g, 72%): $[\alpha]_D$ +42.3° (1.0 g/100 mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.09 (9 H, s, $Si(CH_3)_3$), 1.43 (2 H, d, J = 8.5 Hz, CH_2Si), 1.64 (3 H, s, CH_3C=C), 2.41 (2 H, m, CH_2C=CH), 2.77 (1 H, m, CH_aH_bO), 3.06 (2 H, m, CH_2CO), 3.23 (1 H, m, CH_aH_bO), 4.19 (2 H, m, $CH_2C_6H_5$), 4.68 (1 H, m, C*H*N), 5.29 (1 H, t, J = 8.5 Hz, C=C*H*), 7.22–7.38 (5 H, m, C_6H_5); ^{13}C NMR [1,2-$^{13}C_2$]-**14** ($CDCl_3$) δ 34.41 ($^{13}CH_2$, d, J = 60 Hz), 172.78 (^{13}CO, d, J = 60 Hz); IR λ_{max} ($CHCl_3$) 1780 (C=O), 1695 (C=O) cm^{-1}; EI mass spectrum, *m/e* 359.1898 (calcd for $C_{20}H_{29}NO_3Si$ 359.1917).

(2′*S*,4*S*)-4-Benzyl-*N*-[2′,4′-dimethyl-6′-(trimethylsilyl)-4′-hexenoyl]oxazolidinone (15). A solution of 1.77 mL of diisopropylamine (1.28 g, 12.70 mmol) in THF (80 mL) was stirred and cooled at 0 °C under argon while *n*-butyllithium (2.15 M, 5.90 mL, 12.70 mmol) was added, while the temperature was kept below 5 °C. The reaction mixture was stirred for a further 20 min before being cooled to −78 °C. A solution of the (*S*)-(-)-benzyloxazolidinone derivative **14** (4.60 g, 12.7 mmol) in THF (8 mL) was added slowly, while the temperature was kept below −65 °C. The solution was stirred at −78 °C for a further 30 min, and then methyl iodide (1.6 mL, 3.65 g, 25 mmol) was added. After 30 min the reaction mixture was allowed to warm to −45 °C in an acetonitrile–dry ice bath, stirred for a further 4 h, and then warmed to 0 °C over 1 h. The solution was poured into ethyl acetate (120 mL) and washed with 1 M sodium bisulfate solution (2 × 60 mL), sodium bicarbonate (60 mL), and brine (60 mL). The organic portion was dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil. Column chromatography on silica using 5–7% ethyl acetate in pentane as eluent gave the methylation product **15** as a clear colorless oil (3.294 g, 69%); ^{1}H and ^{13}C NMR indicated that this oil was a single diastereomer:[10,11] $[\alpha]_D$ +51.07° (1.3 g/100 mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.024 (9 H, s, $Si(CH_3)_3$), 1.21 (3 H, d, J = 6.8 Hz, CH_3CHCO), 1.42 (2 H, m, CH_2Si), 1.61 (3 H, s, CH_3C=C), 2.09 (1 H, dd, J = 7.8, 13.4 Hz, $CH_aH_bCHCH_3$), 2.51 (1 H, dd, J = 6.8, 13.4 Hz, $CH_aH_bCHCH_3$), 2.82 (1 H, m, CH_aH_bO), 3.29 (1 H, m, CH_aH_bO), 4.11 (1 H, tq, J = 7 Hz, CH_3CHCO), 4.19 (2 H, m, $CH_2C_6H_5$), 4.67 (1 H, m, C*H*N), 5.28 (1 H, t, J = 8 Hz, C=C*H*), 7.24–7.38 (5 H, m, C_6H_5); ^{13}C NMR [1,2-$^{13}C_2$]-**15** ($CDCl_3$) δ 35.9 (^{13}CH, d, J = 50 Hz), 177.06 (^{13}CO, d, J = 50 Hz); IR λ_{max} ($CHCl_3$) 1780 (C=O), 1695 (C=O) cm^{-1}; EI mass spectrum, *m/e* 373.2129 (calcd for $C_{21}H_{31}NO_3Si$ 373.21305).

(4*E*)-(2*S*)-2,4-Dimethyl-6-(trimethylsilyl)-4-hexenoic Acid (16). To the methylated oxazolidinone derivative **15** (3.29 g, 8.76 mmol) in THF (25 mL) was added a solution of lithium hydroxide (735 mg, 17.52 mmol) in 5 mL of 30% hydrogen peroxide dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then quenched with saturated sodium sulfite solution (5 mL), which was added dropwise with cooling. The mixture was poured into 1 M sodium bisulfate (40 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic portions were dried ($MgSO_4$), filtered, and concentrated. Column chromatography of the re-

sulting oil on silica gel using a 10–40% ethyl acetate–pentane gradient as eluent gave (–)-**16** as a clear, colorless, odorless oil (1.73 g, 97%): $[\alpha]_D$ –4.55° (1.38 g/100 mL, $CHCl_3$); ^1H NMR ($CDCl_3$) δ –0.04 (9 H, s, $Si(CH_3)_3$), 1.11 (3 H, d J = 7 Hz, CH_3CHCO), 1.38 (2 H, d, J = 8 Hz, CH_2Si), 1.55 (3 H, s, $CH_3C{=}C$), 2.04 (1 H, dd, J = 8, 14.8 Hz, CH_aH_bCH), 2.41 (1 H, dd, J = 8, 14.8 Hz, CH_aH_bCH), 2.62 (1 H, m, CH_3CHCO), 5.23 (1 H, t, J = 8 Hz, C=CH), 7.5–13 (1 H, br s, CO_2H); ^{13}C NMR ($CDCl_3$) δ –1.76 (CH_3Si), 15.47 ($CH_3C{=}$), 16.41 (CH_3CH), 18.84 (CH_2Si), 38.05 (CH_3CH), 43.97 ($CH_2C{=}$), 123.37 (CH=C), 128.98 ($C{=}CH$), 183.28 (CO); IR λ_{max} ($CHCl_3$) 3200–2800 (CO_2H), 1710 (C=O) cm^{-1}; EI mass spectrum, m/e 214.1399 (calcd for $C_{11}H_{22}O_2Si$ 214.1389).

(2*S*,4*R*)-2,4-Dimethyl-5-hexenoic Acid (17). To allylsilane acid **16** (1.73 g, 8.62 mmol) in 9 mL of methylene chloride at 0 °C under argon was added dropwise 3 mL of freshly distilled 25% BF_3–AcOH. The reaction mixture was stirred for 15 min, poured into brine (25 mL), and extracted with methylene chloride (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column filtration on silica using 10–40% ethyl acetate–pentane as eluent gave the acid (+)-**17** as a clear, colorless, pungent oil (1.20 g, 98%); ^1H and ^{13}C NMR showed the oil to be an 8:1 mixture of diastereomers: $[\alpha]_D$ +8.13° (1.34 g/100 mL, $CHCl_3$); ^1H NMR (2*S*,4*R*)-**17** (major diastereomer) ($CDCl_3$) δ 1.02 (3 H, d, J = 8 Hz, 4-CH_3CH), 1.15 (3 H, d, J = 8 Hz, CH_3CHCO), 1.34 (1 H, m, CH_aH_b), 1.73 (1 H, m, CH_aH_b), 2.20 (1 H, m, $CHCH{=}CH_2$), 2.47 (1 H, m, $CHCO$), 4.97 (2 H, m, $CH{=}CH_2$), 5.62 (1 H, m, $CH{=}CH_2$), 11–12 (1 H, br s, CO_2H); ^1H NMR (2*S*,4*S*)-**17** (minor diastereomer) ($CDCl_3$) includes δ 0.98 (3 H, d, J = 8 Hz, 4-CH_3CH) and 1.17 (3 H, d, J = 8 Hz, CH_3CHCO); ^{13}C NMR (2*S*,4*R*)-**17** (major diastereomer) ($CDCl_3$) δ 17.68 (CH_3), 20.59 (CH_3), 35.78 (CH), 37.31 (CH), 39.98 (CH_2), 113.54 ($CH{=}CH_2$), 143.41 ($CH{=}CH_2$), 183.07 ($C{=}O$); IR λ_{max} ($CHCl_3$) 3200–2800 (CO_2H), 1710 (C=O) cm^{-1}; CI (CH_4) mass spectrum, m/e 143.1072 (calcd for $C_8H_{15}O_2$ [M + H] 143.107195).

(2*S*,4*R*)-2,4-Dimethyl-5-methylvalerolactone (19). Method A. Mercuric acetate (354 mg, 1.11 mmol) was added to a solution of 160 mg (1.11 mmol) of **17** in 15 mL of THF under argon. The reaction mixture was stirred for 30 min, after which lithium tetrachloropalladate (291 mg, 1.11 mmol) and lithium carbonate (246 mg, 3.33 mmol) were added. The mixture was stirred for a further 2 h. After filtration through Celite and washing with diethyl ether (100 mL), the resulting organic solution was washed with brine (3 × 30 mL), dried ($MgSO_4$), and carefully concentrated. Column chromatography on silica using 4–6% ethyl acetate in cyclohexane as eluent gave the enol lactone **19** as a clear, colorless oil (45–50 mg, 30%).

Method B. Mercuric acetate (276 mg, 0.87 mmol) was added to a solution of 125 mg (0.868 mmol) of **17** in 15 mL of acetonitrile under argon. The reaction mixture was stirred for 1 h and then concentrated under high vacuum. The resulting solid was redissolved in acetonitrile (25 mL), and lithium tetrachloropalladate (230 mg, 0.87 mmol), cupric chloride (120 mg, 0.87 mmol), and freshly activated, ground molecular sieves (1 g) were added. The mixture was stirred for 8 h. After filtration through Celite and washing with diethyl ether (120 mL), the resulting organic solution was washed with brine (3 × 30 mL), dried ($MgSO_4$), and carefully concentrated. Column chromatography on silica using 4% ethyl acetate in hexanes as eluent gave the enol lactone **19** (36 mg, 29%) containing <15% of the 2*S*,4*S* diastereomer as judged by ^{13}C NMR: $[\alpha]_D$ +14° (0.2 g/100 mL, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.19 (3 H, d, J = 8 Hz, 4-CH_3CH), 1.28 (3 H, d, J = 8 Hz, CH_3CHCO), 1.2–1.4 (1 H, m, CH_aH_b), 1.95 (1 H, m, CH_aH_b), 2.6 (2 H, m, $CHC{=}CH_2$ + $CHCO$), 4.28 (1 H, m, C=C*H*H), 4.67 (1 H, m, C=C*H*H); ^{13}C NMR (2*S*,4*R*)-**19** ($CDCl_3$) δ 16.60 (2-CH_3), 18.43 (4-CH_3), 32.32 (4-CH), 35.63 (CH_2), 36.52 (2-CH), 92.37 ($C{=}CH_2$), 160.58 ($C{=}CH_2$), 171.87 ($C{=}O$); ^{13}C NMR (2*S*,4*S*)-**19** ($CDCl_3$) δ 16.75 (2-CH_3), 18.01 (4-CH_3), 29.96 (4-CH), 33.09 (2-CH), 33.95 (CH_2), 92.83 ($C{=}CH_2$), 160.10 ($C{=}CH_2$), 172.60 ($C{=}O$); ^{13}C NMR (2*S*,4*R*)-[1,2-$^{13}C_2$]-**19** ($CDCl_3$) δ 36.52 (d, $^{13}CHCO$), 171.87 (d, $CH^{13}CO$); IR λ_{max} ($CHCl_3$) 1710 (C=O), 1655 ($OC{=}CH_2$) cm^{-1}; UV λ_{max} 240 nm; CI (isobutane) mass spectrum [1,2-$^{13}C_2$]-**22**, m/e 143.0993 (calcd for $^{13}C_2C_6H_{13}O_2$ [M + H] 143.09824).

(2*S*,4*R*)-2,4-Dimethyl-5-oxohexanoyl NAC Thioester (20). The enol lactone **19** (36 mg, 0.253 mmol) was dissolved in THF (15 mL) along with *N*-acetylcysteamine (100 mg, 0.89 mmol) and DBU (50 μL). The reaction mixture was stirred for 30 min at room temperature under argon. Diethyl ether (40 mL) was added, and the organic solution washed with aqueous NH_4Cl solution (2 × 20 mL), water (20 mL), and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography using ethyl acetate as eluent gave the thioester **20** as a clear, colorless oil (45 mg, 71%). ^1H and ^{13}C NMR showed the oil to be an 8:1 mixture of diastereomers. The use of elevated temperatures or more prolonged reaction times led to epimerization at C-2 of the recovered enol lactone and a consequent reduction in the enantiomeric and diastereomeric purity of the resulting thioester: $[\alpha]_D$ +17.3° (0.2 g/100 mL, $CHCl_3$); ^1H NMR (2*S*,4*R*)-**20** ($CDCl_3$) δ 1.11 (3 H, d, J = 8 Hz, 4-CH_3CH), 1.19 (3 H, d, J = 8 Hz, CH_3CHCOS), 1.0–1.2 (1 H, m, CH_aH_b), 1.8–1.9 (1 H, m, CH_aH_b), 1.96 (3 H, s, CH_3CONH), 2.14 (3 H, s, CH_3COCH2), 2.53 (1 H, m, $CHCH_3COCH_3$), 2.68 (1 H, m, $CHCH_3COS$), 3.00 (2 H, m, CH_2S), 3.42 (2 H, m, CH_2NH), 6.0 (1 H, br s, N*H*); ^{13}C NMR (2*S*,4*R*)-[1,2-$^{13}C_2$]-**20** ($CDCl_3$) δ 46.44 (d, J = 45 Hz, $^{13}CHCO$), 203.51 (d, J = 45 Hz, $CH^{13}CO$). ^{13}C NMR (2*S*,4*S*)-[1,2-$^{13}C_2$]-**20** ($CDCl_3$) δ 46.34 (d, J = 45 Hz, $^{13}CHCO$), 203.75 (d, J = 45 Hz, $CH^{13}CO$); IR λ_{max} ($CHCl_3$) 3400 (br, NH), 1710 (C=O), 1670 (SC=O + NHC=O) cm^{-1}; EI mass spectrum, m/e 260.1326 (calcd for $C_{12}H_{22}NO_3S$ [M + H] 260.13202).

(2*S*,4*R*)-*N*-Methyl-*N*-methoxy-2,4-dimethyl-5-hexenamide (21). Carbonyl diimidazole (150 mg, 0.92 mmol) was reacted for 1.5 h under argon with 131 mg (0.923 mmol) of unlabeled (+)-**17**. *N*-methyl-*N*-methoxylamine hydrochloride (180 mg, 1.85 mmol) and triethylamine (0.3 mL) were added, and the mixture was stirred overnight. The reaction mixture was partitioned between diethyl ether (60 mL) and 0.1 M hydrochloric acid (30 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography on silica, using 10% ethyl acetate in pentane as eluent, gave the amide **21** as a clear colorless oil (84 mg, 50%): $[\alpha]_D$ +13.75°; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz, CH_3CH), 1.07 (3 H, d, J = 7 Hz, CH_3CH), 1.3 (1 H, m, CH_aH_b), 1.65 (1 H, m, CH_aH_b), 2.15 (1 H, m, $CHCH_3$), 2.87 (1 H, m, $CHCH_3$), 3.12 (3 H, s, NCH_3), 3.63 (3 H, s, $NOCH_3$), 4.92 (2 H, m, $CH{=}CH_2$), 5.60 (1 H, m, $CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 17.09 (CH_3), 20.81 (CH_3), 32.34 (NCH_3), 32.97 (CH), 36.06 (CH), 40.32 (CH_2), 61.35 (OCH_3), 112.97 ($CH{=}CH_2$), 144.05 ($CH{=}CH_2$), (C=O not observed); IR λ_{max} ($CHCl_3$) 1645 (C=O) cm^{-1}.

(2*E*)-(4*S*,6*R*)-Methyl 4,6-Dimethylocta-2,7-dienoate (24). To 290 mg (1.57 mmol) of **21** in 30 mL of THF at 0 °C under argon was added 3.13 mL (3.13 mmol) of a 1 M THF solution of diisobutylaluminum hydride. The mixture was stirred for 1 h at 0 °C and then poured into pH 7.4 buffer (60 mL). The aqueous solution was saturated with sodium chloride and filtered through a sintered-glass filter under vacuum. The filtrate was extracted with chloroform (3 × 30 mL), and the combined organic layers were dried ($NaSO_4$), filtered, and partially concentrated to about 50 mL, to give a solution of the aldehyde **22**.

A solution of [1,2-$^{13}C_2$]-**23** (99 atom % ^{13}C) was generated from the corresponding phosphonium bromide (635 mg, 1.57 mmol) by shaking a chloroform solution of the salt with 1 M sodium hydroxide, drying ($MgSO_4$), and filtering. The resulting ylide was partially concentrated to about 30 mL and added to the solution of the aldehyde **22**. The mixture was heated at reflux for 6 h under argon and then cooled and concentrated. The crude oil was filtered through silica, using 5% diethyl ether in pentane as eluent, to remove polar byproducts. The concentrated filtrate was purified by TLC, using 3% diethyl ether in pentane as eluent, to give [1,2-$^{13}C_2$]-**24** as a clear, colorless oil (130 mg, 45%), which was shown to be an 8:1 mixture of the desired 4*S*,6*R* diastereomer and the corresponding 4*S*,6*S* diastereomer by ^{13}C NMR: $[\alpha]_D$ +31.96°; ^1H NMR [1,2-$^{13}C_2$]-**24** ($CDCl_3$) δ 0.95 (3 H, d, J = 7 Hz, CH_3CH), 1.01 (3 H, d, J = 7 Hz, CH_3CH), 1.23 (1 H, m, CH_aH_b), 1.65 (1 H, m, CH_aH_b), 2.12 (1 H, m, $CHCH_3$), 2.34 (1 H, m, $CHCH_3$), 3.70 (3 H, d, J_{COCH} = 4 Hz, OCH_3), 4.90 (2 H, m, $CH{=}CH_2$), 5.75 (1 H, dddd, J_{CH} = 162 Hz, J_{CCH} = 3 Hz, J = 1, 15.8 Hz, $^{13}CH{=}CH$), 5.60 (1 H, m, $CH{=}CH_2$), 6.8 (1 H, m, $^{13}CH{=}CH$); ^{13}C NMR (4*S*,6*R*)-[1,2-$^{13}C_2$]-**24** ($CDCl_3$) δ 119.01 ($^{13}CH{=}CH$, d, J = 75 Hz), 162.27 ($^{13}C{=}O$, d, J = 75 Hz); ^{13}C NMR (4*S*,6*S*)-[1,2-$^{13}C_2$]-**24** ($CDCl_3$) δ 119.51 ($^{13}CH{=}CH$, d, J = 75 Hz), 162.27 ($^{13}C{=}O$, d, J = 75 Hz); IR λ_{max} ($CHCl_3$) 1670 (C=O), 1625 (C=C, weak) cm^{-1}.

(2*E*)-(4*S*,6*R*)-4,6-Dimethylocta-2,7-dienoic Acid (25). To 130 mg (0.71 mmol) of **24** in 3 mL of ethanol was added a solution of 60 mg (1.1 mmol) of potassium hydroxide in 2 mL of ethanol. The mixture was heated at reflux for 1.5 h. After concentration to 2 mL, the mixture was poured into 1 M HCl (20 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Column chromatography on silica, using 15–25% ethyl acetate in pentane as eluent, gave the α,β-unsaturated acid **25** as a colorless oil (63 mg, 52%), which was shown to be an 8:1 mixture of the desired 4*S*,6*R* diastereomer and the corresponding 4*S*,6*S* diastereomer by ^{13}C NMR: $[\alpha]_D$ +40.30°; ^1H NMR [1,2-$^{13}C_2$]-**25** ($CDCl_3$) δ 0.97 (3 H, d, J = 6 Hz, CH_3CH), 1.03 (3 H, d, J = 6 Hz, CH_3CH), 1.24 (1 H, m, CH_aH_b), 1.42 (1 H, m, CH_aH_b), 2.17 (1 H, m, $CHCH_3$), 2.39 (1 H, m, $CHCH_3$), 4.94 (2 H, m, CH=CH_2), 5.77 (1 H, dm, J_{CH} = 160 Hz, ^{13}CH=CH), 5.61 (1 H, m, CH=CH_2), 6.97 (1 H, m, ^{13}CH=CH), 10–13 (1 H, very broad, CO_2H); ^{13}C NMR (4*S*,6*R*)-[1,2-$^{13}C_2$]-**25** ($CDCl_3$) δ 118.81 (^{13}CH=CH, d, J = 72 Hz), 172.27 (^{13}C=O, d, J = 72 Hz); ^{13}C NMR (4*S*,6*S*)-[1,2-$^{13}C_2$]-**25** ($CDCl_3$) δ 119.29 (^{13}CH=CH, d, J = 72 Hz), 172.27 (^{13}C=O, d, J = 72 Hz); IR λ_{max} ($CHCl_3$) 3300–2900 (CO_2H), 1655 (C=O), 1620 (C=C, weak) cm^{-1}; EI mass spectrum [1,2-$^{13}C_2$]-**25**, m/e 170.1210 (calcd for $^{13}C_2C_8H_{16}O_2$ 170.12172).

(2*E*)-(4*S*,6*R*)-4,6-Dimethyl-7-oxo-2-octenoic Acid (26). Mercuric acetate (87 mg, 0.27 mmol) was added to 42 mg (0.25 mmol) of **25** in 5 mL of methanol, and the mixture was stirred for 1 h. A solution of lithium tetrachloropalladate (70 mg, 0.271 mmol) in methanol (5 mL) was added, and the mixture was stirred for an additional 2.5 h. After addition of 2 mL of 1 M HCl and stirring continued for a further 30 min, the reaction mixture was diluted with ethyl acetate (60 mL) and washed with brine (4 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography on silica, using a gradient of 30–100% ethyl acetate in pentane as eluent, gave the ketonic acid **26** as a clear colorless oil (21.5 mg, 47%) along with some starting material **25** (11 mg, yield based on recovered starting material was 63%). The ratio of the desired 4*S*,6*R* enantiomer to the 4*S*,6*S* diastereomer was estimated to be ca. 8:1 by ^{13}C NMR analysis, indicating that no significant epimerization at either C-4 or C-6 had occurred during formation of the ketone: ^1H NMR [1,2-$^{13}C_2$]-**26** ($CDCl_3$) δ 1.07 (3 H, d, J = 6 Hz, CH_3CH), 1.09 (3 H, d, J = 6 Hz, CH_3CH), 1.34 (1 H, m, CH_aH_b), 1.81 (1 H, m, CH_aH_b), 2.12 (3 H, s, CH_3CO), 2.34 (1 H, m, CH=CHCHCH$_3$), 2.47 (1 H, m, $CH_3COCHCH_3$), 5.78 (1 H, dm, J_{CH} = 164 Hz, ^{13}CH=CH), 6.87 (1 H, m, ^{13}CH=CH); ^{13}C NMR (4*S*,6*R*)-[1,2-$^{13}C_2$]-**26** ($CDCl_3$) δ 119.72 (^{13}CH=CH, d, J = 73 Hz), 171.61 (^{13}C=O, d, J = 73 Hz); ^{13}C NMR (4*S*,6*S*)-[1,2-$^{13}C_2$]-**26** ($CDCl_3$) δ 119.65 (^{13}CH=CH, d, J = 73 Hz), 171.61 (^{13}C=O, d, J = 73 Hz).

(2*E*)-(4*S*,6*R*)-4,6-Dimethyl-7-oxo-2-octenoyl *N*-Acetylcysteamine Thioester (27). To 21.5 mg (0.12 mmol) of **26** in 5 mL of dimethylformamide under argon was added 37 mg (0.35 mmol) of freshly prepared *N*-acetylcysteamine along with 64 mg (0.23 mmol) of diphenyl phosphorazidate and 3 drops of triethylamine. The reaction mixture was stirred overnight at room temperature, diluted with ethyl acetate (50 mL), and washed with water (4 × 20 mL) and brine (20 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated. Preparative thin-layer chromatography on silica using ethyl acetate as eluent gave **27** (14 mg, 44%). The ratio of the desired 4*S*,6*R* enantiomer to the 4*S*,6*S* diastereomer was established as 8:1, based on the ratio of the CH_3COCH peaks in the ^1H NMR spectrum: $[\alpha]_D$ +32.85°; ^1H NMR (4*S*,6*R*)-[1,2-$^{13}C_2$]-**27** ($CDCl_3$) δ 1.06 (1 H, d, J = 6 Hz, CH_3CH), 1.09 (1 H, d, J = 6 Hz, CH_3CH), 1.34 (1 H, m, CH_aH_b), 1.81 (1 H, m, CH_aH_b), 1.95 (3 H, s, CH_3CON), 2.10 (3 H, s, CH_3CO), 2.31 (1 H, m, CH=CHCHCH$_3$), 2.48 (1 H, m, $CH_3COCHCH_3$), 3.07 (2 H, m, NCH_2), 3.43 (2 H, m, SCH_2), 6.06 (1 H, ddd, J_{CH} = 164 Hz, J_{CCH} = 5 Hz, J = 16 Hz, ^{13}CH=CH), 5.96 (1 H, br s, NH), 6.70 (1 H, m, ^{13}CH=CH); ^1H NMR (4*S*,6*S*)-[1,2-$^{13}C_2$]-**27** ($CDCl_3$) shows δ 2.11 (3 H, s, CH_3CO); ^{13}C NMR [1,2-$^{13}C_2$]-**27** ($CDCl_3$) δ 127.14 (^{13}CH=CH, d, J = 61 Hz), 190.13 (^{13}C=O, d, J = 61 Hz); IR λ_{max} ($CHCl_3$) 1705, 1665, 1630 (C=O), 1600 (C=C, weak) cm^{-1}; EI mass spectrum [1,2-$^{13}C_2$]-**27**, m/e 288.1535 (calcd for $^{13}C_2C_{12}H_{24}NO_3S$ [M + H] 288.15437).

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Registry No. **1**, 17090-79-8; [2,3-$^{13}C_2$]-**6**, 77504-81-5; [2,3-$^{13}C_2$]-**7**, 116078-25-2; [2,3-$^{13}C_2$]-**8**, 116078-60-5; [2,3-$^{13}C_2$]-**9**, 116078-26-3; [2,3-$^{13}C_2$]-**10**, 116078-27-4; [2,3-$^{13}C_2$]-**11**, 80399-29-7; **12**, 116078-52-5; [1′,2′-$^{13}C_2$]-**12**, 116078-28-5; **13**, 116078-53-6; [1,2-$^{13}C_2$]-**13**, 116078-29-6; **14**, 116078-54-7; [1,2-$^{13}C_2$]-**14**, 116078-30-9; (*R*)-**14**, 116078-51-4; **15**, 116078-55-8; [1,2-$^{13}C_2$]-**15**, 116078-31-0; **16**, 116179-64-7; [1,2-$^{13}C_2$]-**16**, 116078-32-1; (2*S*,4*R*)-**17**, 116179-65-8; [1,2-$^{13}C_2$]-(2*S*,4*R*)-**17**, 116078-33-2; (2*S*,4*S*)-**17**, 116179-66-9; [1,2-$^{13}C_2$]-(2*S*,4*S*)-**17**, 116078-44-5; (2*R*,4*S*)-**17**, 116179-61-4; (2*R*,4*S*)-**17** (methyl ester), 116179-63-6; (−)-**18**, 82917-27-9; (2*S*,4*R*)-**19**, 116078-56-9; [2,3-$^{13}C_2$]-(2*S*,4*R*)-**19**, 116078-34-3; (2*S*,4*S*)-**19**, 116179-67-0; [2,3-$^{13}C_2$]-(2*S*,4*S*)-**19**, 116179-62-5; (2*S*,4*R*)-**20**, 116078-57-0; [1,2-$^{13}C_2$]-(2*S*,4*R*)-**20**, 116078-35-4; (2*S*,4*S*)-**20**, 116078-59-2; [1,2-$^{13}C_2$]-(2*S*,4*S*)-**20**, 116078-45-6; **21**, 116078-36-5; **22**, 82917-23-5; [1,2-$^{13}C_2$]-**23**, 116078-37-6; [1,2-$^{13}C_2$]-(4*S*,6*R*)-**24**, 116078-38-7; [1,2-$^{13}C_2$]-(4*S*,6*S*)-**24**, 116078-48-9; [1,2-$^{13}C_2$]-(4*S*,6*R*)-**25**, 116078-39-8; [1,2-$^{13}C_2$]-(4*S*,6*S*)-**25**, 116078-49-0; [1,2-$^{13}C_2$]-(4*S*,6*R*)-**26**, 116078-40-1; [1,2-$^{13}C_2$]-(4*S*,6*S*)-**26**, 116078-50-3; [1,2-$^{13}C_2$]-(4*S*,6*R*)-**27**, 116078-41-2; [1,2-$^{13}C_2$]-(4*S*,6*S*)-**27**, 116179-60-3; $AcNHCH_2CH_2SCO^{13}C(CO_2Me)_2Me$, 116078-42-3; $MeO^{13}CO^{13}CH_2Br{\cdot}PPh_3$, 116078-47-8; sodium [2-^{13}C]propionate, 83587-76-2; [2-^{13}C]propionyl chloride, 106588-66-3; *N*-acetylcysteamine, 1190-73-4; [2-^{13}C]acetyl chloride, 14770-40-2; sodium [1,2-$^{13}C_2$]acetate, 56374-56-2; sodium acetate, 127-09-3; acetyl chloride, 75-36-5; *tert*-butyldimethylsilanol, 18173-64-3; (*E*)-*N*-[4′-methyl-6′-(trimethylsilyl)-4-hexenoyl]-imidazole, 116078-58-1; [1′,2′-$^{13}C_2$]-(*E*)-*N*-[4′-methyl-6′-(trimethylsilyl)-4-hexenoyl]imidazole, 116078-43-4; (4*S*)-(−)-benzyloxazolidinone, 90719-32-7; [1,2-$^{13}C_2$]acetyl chloride, 89186-79-8.